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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/380,579	09/07/1999	SUSUMU IKEHARA	Q55691	2802

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EXAMINER	
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ART UNIT	PAPER NUMBER
1644	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/380,579	IKEHARA ET AL.	
	Examiner	Art Unit	
	Michail A. Belyavskyi	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 August 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *8 and 9* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *8 and 9* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

RESPONSE TO APPLICANT'S AMENDMENT

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 08/21/07 has been entered.

Claims 9 and 10 are pending.

In view of the amendment, filed 08/21/07 the following rejection remains:

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 9 and 10 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a New Matter rejection.**

" engraftment rate of 100 % for more than 13 weeks " and " reducing graft rejection in any organ transportation recipient, wherein graft donor is a different animal of the same species of recipient" claimed in claim 9 represent a departure from the specification and the claims as originally filed. The passages pointed by the applicant do not provide a clear support for the general terms "over a period of **for more than 13 weeks**" and "reducing graft rejection in any organ transportation recipient, wherein graft donor is a different animal of the same species of recipient" The specification and the claims as originally field only support " engraftment rate of 100 % **up to 13 week**.

Applicant's arguments filed 08/21/07 have been fully considered, but have not been found convincing.

Applicant's asserts that : (i) the expression "more than 13 weeks" is supported the at page 28, lines 10-16 of the Specification (ii) Support for 100% engraftment "more than" 13 weeks" can be

found in Fig. 2.; (iii) the mouse model in Example 4 is a well recognized model for human and thus Example 4 reasonably conveys to one skill in the art "any organ transplantation"; (iv) As stated in the declaration by Dr. Ikehara, if a new strategy is to be proved useful for skin and islet transplantation, it is generally accepted to one skill in the art that this strategy could be applicable to all organ/tissue transplantation.

Contrary to Applicant's assertion, the Specification on page 28, lines 10-16 explicitly disclosed that " successful engraftment was obtained in 3 of 3 recipient mice in the portal administration group **at week 13** after transplantation" (emphases added). It is the Examiner position, that said teaching of the Specification only supports " engraftment rate of 100 % **up to 13 week** , not **more than 13 weeks**.

With regards to Applicant's comments that "Support for 100% engraftment more than 13 weeks" can be found in Fig. 2.

The date in Fig.2, represents very specific example , wherein 100% skin engraftment has been achieved in mice, wherein Balb/c mice has been used as a donor and B6 mice has been used as a recipient. However, said specific example does not provide a support for a general claimed 100% engraftment in any organ transplantation in any recipient, as claimed in amended claim 1. In re Smith, 173 USPQ 679-----Where it was ruled that a genus may not support a subgenus even though there is a disclosed species within the subgenus.

With regards to the issue that the mouse model in Example 4 is a well recognized model for human and thus Example 4 reasonably conveys to one skill in the art "any organ transplantation" and statement in declaration by Dr. Ikehara that if a new strategy is to be proved useful for skin and islet transplantation, it is generally accepted to one skill in the art that this strategy could be applicable to all organ/tissue transplantation.

It is noted that the instant claims 9 and 10 are rejected under 35 U.S.C. 112, first paragraph, **new matter rejection** not enablement rejections. At best Declaration by Dr. Ikehara indicates that it might be obvious to one skill in the art that claimed strategy might be applicable to various organ/tissue transplantation. However, obviousness is not the standard for the addition of new limitations to the disclosure as filed. It is noted that entitlement to a filing date does not extend to subject matter which is not disclosed, but would be obvious over what is expressly disclosed. Lockwood v. American Airlines Inc., 41 USPQ2d 1961 (Fed. Cir. 1977). New Matter is a written description issue.

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

5. Claims 9-10 stand rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent 6,428,782 in view of US Patent. No. 5,514,364, Zhang et al. (Eur. J. Immunol. 24 :1558-1565, IDS) and US Patent 5,876708 for the same reasons set forth in the previous Office Action mailed on 08/09/07.

Applicant's arguments, filed 08/21/07 have been fully considered, but have not been found convincing.

Applicant asserts that: (i) the Examiner continues to overlook Applicant's arguments that there is no motivation, suggestions or teaching in the prior art to combine the references (ii) Only US Patent'364 teaches using TBI within the range claimed; (iii) while US Patent'364 may teach that allogeneic engraftment was reliably achieved in 100% of all animals conditioned with 7 Gy, this related to engraftment of donor BMC not to engraftment of donor transplanted organ; A 100% engraftment rate for BMC does not lead to 100% organ engraftment; (iv) In Fig.7, US Patent 364 disclosed that 100% engraftment of skin was achieved only during allogeneic transplantation. The amended claim 9 now recites that the donor is a different animal of the same species as the recipient; (v) US Patent'782 teaches that only BMC achieved 100% engraftment, not "organ grafts". The only 100% of skin graft has been achieved when TLI, not TBI has been used in US Patent '782; Moreover, US Patent '782 teaches that TLI is preferred over TBI, and further that in view of Fig.2 US Patent '782 , that shown the decreasing in the survival rate with the increasing the dose of irradiation, one skill in the art would never think of increasing the dose of TBI and would not have been motivated to combine the teaching of US Patent' '782 and US patent 364; (vi) In Fig. 5, 7 and 20 of US Patent '782 the BMC, spleen cells and the like are not "organ" grafts, as claimed in the present invention; (vii) US Patent'708, disclosed 4.0 Gy of TBI, the same as disclosed by US Patent'782, thus a person skilled in the art would expect the same level of effects as achieved by US Patent '782; (viii) Zhang et al., describes the effects of intravenous and portal venous administrations of bone marrow cells on prolonged graft survival, however, even if US Patent'782 was combined with Zhang et al., a person skilled in the art could neither predict therefrom whether the excellent immunological tolerance-inducing effect as achieved by the present invention could be achieved,

nor foresee how irradiation before portal venous administration could affect immunological tolerance-inducing effects.

It has been recently stated that KSR forecloses the argument that a specific teaching, suggestion, or motivation are required to support a finding of obviousness See Board decision (see *KSR International Co v Teleflex Inc.*, 550U.S.-, 82 USPQ2d 1385, 2007).

It appears that applicant and the examiner differ on interpretation of both the claimed methods and the prior art. As has been stated in the previous Office Action, it is the Examiner position, that US Patent '782 teaches a method for reducing graft rejection in an organ allograft and xenograft transplantation by subjecting the recipient to sublethal total body irradiation (TBI) and administering to the recipient whole bone marrow. Applicants attention is respectfully directed to column 8, lines 57-67, where it is specifically stated that " if TBI is used it should be at a dose level that causes no servere or irreversible pancytopenia. US Patent '782 teaches that transplanting of organ into recipient occurs within the same day as whole bone cells are administered (see column 13, lines 50-67, column 14, lines 10-15 and Example 14 in particular). US Patent '782 teaches that engraftment rate of 100 % is achieved (see Fig, 5, 7, 17, 20, Tables I -III example 14 in particular). Moreover, the Examiner disagree with Applicant in that "based on the data presented in US Patent '782 a person skilled in the art could not predict an engraftmernt rate of 100". The data presented in Fig. 4 and 7 only shown cumulative data from experiments to determine the GVL activity across an incompatibility involving both MHC and MiHL alloantigens. The Specification in Table 1-3 disclosed data that skin allografts survived for more than 100 days in all mice. In Example 14, it is explicitly stated that 100% of BM stromal grafts and approximately 80 % of the heart graft survived. However, it is further disclosed that by simply **altering doses** of treatment , including doses of radiation, might be beneficial to achieve better engraftment (emphases added).

With regards to Applicant's statement that a person skilled in the art would expect the same level of effects as achieved by US Patent '782. As has been acknowledge by Applicant, TBI taught by US Patent '782 was conducted at dose of 4.0 Gy which is much less than claimed in the present invention. Thus skilled artisan could appreciate that a higher dose of TBI might be beneficial and would result in higher engraftment rate, as taught by US Patent '708.

With regards to Applicant statement that "in view of Fig.2 of US Patent '782 wherein increasing the dose of irradiation reduces survival a person skilled in the art would never think of increasing the dose of TBI in the method disclosed in US Patent' 782".
The data presented in Fig.2 was obtained using **TLI irradiation**, not TBI . Clearly one skill in the art would know the difference between these two treatments. Moreover, skilled artisan could appreciate that a higher dose of TBI might be beneficial as taught by US Patent '708. In addition, US Patent'364 explicitly teaches that the dose of TBI administered directly correlates with the engraftment rate. At doses below 6.0 Gy less than 50 % engraftment can be achieved, however, **increasing the doses** up to 7.0 Gy results in 100% ingraftment (see column 17, lines

5-25 in particular). It is the Examiner position that at the time the invention was made one skilled in the art would thinks of increasing the dose of TBI in the method disclosed in US Patent'782.

With regards to Applicant's statement that In Fig. 5, 7 and 20 of US Patent '782 the BMC, spleen cells and the like are not "organ" grafts, as claimed in the present invention.
It is noted that US patent'782 does not limited the invention to BMC or spleen cell transplantation. As clearly stated in column 2 of US '782, the invention provides a **new method to induce transplantation tolerance to cell, tissue and organ allografts and xenorgafts** (emphases added).

US Patent '782 does not teaches the sublethal total body irradiation of at least 6.5 Gy or 7.0 Gy , or that said irradiation is performed one day prior to administration of whole bone marrow cells (newly claimed in claim 9), or administering of whole bone marrow cells by hepatic portal administration.

US Patent '364 teaches and claims a method of conditioning of a recipient intended for organ grafting by subjecting the recipient to sublethal total body irradiation and administering to the recipient whole bone marrow (see entire document, but especially the claims and columns 5, 8, 17 and 21-22). Applicant's attention is respectfully directed to column 9, lines 15-20 where it is explicitly stated that " the importance of the hematopoietic niches or "space" contributed by the low dose of TBI is even more evident when TBI is given one week prior to bone marrow transplantation...". Clearly one skill in the art would interpret said statement as an evidence of the advantage of using TBI .

With respect to the issue that US Patent '364 relates to a technique using mixed chimerism not allogenic chimerism. Applicant's attention is respectfully directed to column 9, line 5-10 and column 19, lines 15-45, wherein it is clearly stated that US Patent '364 invention uses allogenic chemerism as well. Moreover, US Patent '364 also teaches that bone marrow engraftment after sublethal total body irradiation is reliably achieved in 100% of recipients at 7.0 Gy (see Figure 1 and column 17, especially lines 4-25). With regards to Applicant's comments that Fig.7 does not show a 100% acceptance of skin grafts after 19 days. Applicant's attention is respectively drawn to Fig.7 for date on B10, wherein 100% engraftment rate has been achieved beyond day 19. It is noted that the US Patent '364 teaches that grafts were followed for a minimum of 35 days. There are no data that shows that after that time grafts were rejected. Moreover, Applicant's attention is respectively drawn column 17, lines 5-25. It is explicitly disclosed that allogeneic engraftment **was reliably achieved in 100 %.** US '364 further teaches transplantation of organs to the bone marrow recipient and exemplifies skin transplantation, showing that the recipients are specifically tolerant of the donor-type skin (see e.g., Abstract and columns 21-22).

With regards to the comments that In Fig.7, US Patent 364 disclosed that 100% engraftment of skin was achieved only during allogeneic transplantation. The amended claim 9 now recites that the donor is a different animal of the same species as the recipient.

It is noted that US Patent'364 does not limit the invention to only allogeneic transplantation of BMC, but also to induce tolerance for solid organ, tissue and cellular transplantation (see Abstract in particular). Moreover, in Fig.1, US Patent 364 disclosed a data for engraftment with allogeneic and xenogeneic BMC as a function of TBI. Based on the data, one skilled in the art would immediately recognized that increasing a dose of TBI from 4, 0 to 6.5 directly correlates with increasing xenogeneic engraftment rate.

Zhang et al. teach that in both intravenous and portal vein injections of bone marrow cells (BMC), most of the cells migrate to the liver, although more BMC do so after portal vein administration than after intravenous administration (see entire document, especially Figures 3 and 5 and page 1563 at the 4th full paragraph). Zhang et al. also review the art recognized prolongation of organ graft survival in a recipient when cells from the donor are administered to the recipient via the portal vein in addition to the transplanted organ, and note that this is due to a form of immunological tolerance (see especially the "Introduction" on page 1558 and the 1st paragraph of "Discussion" on page 1563).

With regards to Applicants comments about Zhang et al., reference.

Zhang et al., reference has been used by the examiner to show that at the time the invention was made, one skill in the art would know that administration of BMC by hepatic portal venous injection provide an improved method for inducing immunological tolerance in an organ transplantation recipient, and thus would be motivated to used said method.

US Patent '708 teaches a method of inducing immunological tolerance in an organ transplantation recipient, including a step of subjecting the recipient to total body irradiation (TBI) prior to administering to the recipient tolerogen effective amount of bone marrow cells (BMC) (see entire document, Abstract and column 1, lines 25-45, column 3, lines 45-60 and column 9, lines 1-10 in particular). US Patent '708 teaches that said total body irradiation can be performed one day prior to administration of bone marrow cells (see column 9, lines 5-65, column 38, lines 25-60 in particular). US '708 teaches that administration of TBI one day prior to administering BMC is necessary to eliminate recipient's endogenous BMC to stimulate hematopoiesis of the newly introduced foreign BMC.

With regards to Applicant's comments that US Patent'708, disclosed 4.0 Gy of TBI, the same as disclosed by US Patent'782, thus a person skilled in the art would expect the same level of effects as achieved by US Patent '782.

As has been discussed supra, it is the Examiner position that at the time the invention was made one skilled in the art would know that the rate of engraftment depends on the dose of TBI and would be motivated to increase a dose of TBI to achieve a better rate. It is noted that said reference has been used to provide a teaching of a general strategy of subjecting the recipient to total body irradiation using a sublethal dose, prior to administering a BMC, in a method of reducing GVHD during allogeneic or xenogeneic organ transplantation.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to apply the teaching of US Patent '364, US Patent '708 and Zhang et al., to those of US Patent '782 to obtain a claimed method comprising administering to an organ transplant recipient total body sublethal irradiation of at least 6.5 Gy or 6.5 Gy to 7.0 Gy, wherein said irradiation is performed one day prior to administration of whole bone marrow cells and administering whole bone marrow cells by hepatic portal administration.

One of ordinary skill in the art at the time the invention was made would have been motivated to combine sublethal TBI about 7.0 Gy as taught by US Patent '364 and performing said irradiation one day prior to administration of BMC, as taught by US Patent '708 and administration of the bone marrow cells via the hepatic portal vein to provide an improved method for inducing immunological tolerance in an organ transplantation recipient, as taught by Zhang et al., with a method of inducing immunological tolerance in an organ transplantation recipient, taught by US Patent '782. Finally, given the art recognized time constraints associated with transplanting cells and organs from the same human donor; one of ordinary skill in the art would have also been motivated to transplant the organ within the same day as the whole bone marrow cells. The strongest rationale for combining references is a recognition, expressly or impliedly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent, that some advantage or expected beneficial result would have been produced by their combination. In re Semaker. 217 USPQ 1, 5 - 6 (Fed. Cir. 1983). See MPEP 2144. Further, it has been held that where the general conditions of a claim are disclosed in the prior art, discovering the optimum or workable ranges involves only routine skill in the art. *In re Aller*, 220 F2d 454,456,105 USPQ 233; 235 (CCPA 1955). see MPEP § 2144.05 part II A.

Thus, all the claimed elements were known in the prior art and one skill in the art could have combine the elements as claimed by known methods with no change in their respective function and the combination would have yield predictable results to one of ordinary skill in the art at the time of the invention (see *KSR International Co v Teleflex Inc.*, 550U.S.-, 82 USPQ2d 1385, 2007).

Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

6. No claim is allowed.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michail Belyavskyi whose telephone number is 571/ 272-0840 The examiner can normally be reached Monday through Friday from 9:00 AM to 5:30 PM. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on 571/ 272-0841 .

The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

MICHAIL BELYAVSKYI, PH.D.
PATENT EXAMINER

10/25/07